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Ethanol consumption impairs vestibulo-ocular reflex function measured by the video head impulse test and dynamic visual acuity

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Abstract

Ethanol affects many parts of the nervous system, from the periphery to higher cognitive functions. Due to the established effects of ethanol on vestibular and oculomotor function, we wished to examine its effect on two new tests of the vestibulo-ocular reflex (VOR): the video head impulse test (vHIT) and dynamic visual acuity (DVA). We tested eight healthy subjects with no history of vestibular disease after consumption of standardized drinks of 40% ethanol. We used a repeated measures design to track vestibular function over multiple rounds of ethanol consumption up to a maximum breath alcohol concentration (BrAC) of 1.38‰. All tests were normal at baseline. VOR gain measured by vHIT decreased 25% by the highest BrAC level tested in each subject. Catch-up saccades were negligible at baseline and increased in number and size with increasing ethanol consumption (from 0.13° to 1.43° cumulative amplitude per trial). DVA scores increased by 86% indicating a deterioration of acuity, while static visual acuity (SVA) remained unchanged. Ethanol consumption systematically impaired the VOR evoked by high-acceleration head impulses and led to a functional loss of visual acuity during head movement.

Keywords

Ethanol – Vestibular – Video Head Impulse Test – Dynamic Visual Acuity – Vestibulo-Ocular Reflex (VOR) – Saccade.

Introduction

Ethanol has significant effects on vestibular and oculomotor function. Studies have demonstrated reduced reactivity of the ocular motor and vestibular systems after ethanol consumption, including impaired saccadic and pursuit eye movements, nystagmus and vestibulo-ocular reflex (VOR) function. Early studies found that ethanol consumption delays the onset and decreases the peak velocity of saccades, while smooth pursuit becomes increasingly saccadic [1-3, 12, 29]. The slow phase velocity of nystagmus evoked by rotational or caloric stimulation decreases with ethanol [4, 6, 19, 24], as does the slow phase velocity of optokinetic nystagmus [1, 24]. The gaze-holding mechanism is also impaired, causing gaze-evoked nystagmus, which shows increasing velocity with increasing levels of intoxication [5, 10]. More recent studies have investigated the effects of ethanol on otolith function, by testing ocular counterrolling [8, 17], perception of subjective visual horizontal (SVH) [15, 30] and vestibular evoked myogenic potentials [6], albeit with no consistent effect.

One of the most important functions of the vestibulo-ocular system is the VOR, which enables visual stabilization during head motion. Previous studies of the VOR have been based mainly on whole-body rotation and caloric stimulation, which produce continuous vestibular stimulation and evoke nystagmus. The dampening effect of ethanol on the slow phase velocity of vestibular nystagmus is now well-accepted [4, 6, 19, 24]. In contrast, the VOR can also be evoked by more physiological, transient, high-acceleration stimuli, called “head impulses” [11]. In the head impulse test (HIT), when the VOR is intact, subjects are able to maintain gaze on a target during unexpected, brief accelerations of the head. However, if the VOR is deficient, gaze is no longer held on target by the reflex (producing a low VOR gain, or eye velocity/head velocity ratio) and subjects must instead use voluntary “catch-up” saccades to stabilise their vision. Recent advances in technology have led to the development of a video head impulse test (vHIT), which provides a validated measure of head impulses, enabling quick and non-invasive measurement of the VOR under high acceleration conditions [16]. We therefore wished to investigate the effect of ethanol intoxication on the high-acceleration VOR as measured by the vHIT. Due to the ease of testing with video goggles, we were able to make multiple

measurements in each subject over time to track deterioration of VOR with increasing intoxication.

A further aim was to test the potential functional effects of a VOR deficit following ethanol consumption. Impairment of the VOR leads to a reduction of effective vision during head rotations, because retinal shift above 2-4 °/s reduces visual acuity [2, 7]. Compared to visual acuity recorded with the head still (static visual acuity, SVA), acuity recorded during head movement (dynamic visual acuity, DVA) is reduced due to the failure of the VOR to stabilise gaze. Previous research has shown that ethanol reduces DVA during vertical linear sinusoidal acceleration [21, 22]. Subjects showed a raised acuity threshold and an increase in errors following a single dose of ethanol and blood ethanol levels ranging from 0.09 to 0.94 ‰ (per mill) [21]. We aimed to extend these findings by investigating the effects of ethanol on DVA recorded during unpredictable, high acceleration head impulses. We compared the VOR and DVA tests at increasing levels of intoxication up to a higher maximum of 1.38 ‰.

Methods

Eight healthy subjects (mean 27 years, range 25 – 39, 3 females) volunteered for the study. All participants gave written informed consent to participate and the protocol was approved by the local ethics committee (Kantonale Ethik-Kommission Zurich, 2010-0468) in accordance with the sixth revision of the Helsinki declaration (Seoul, Korea 2008). The volunteers reported no history of vestibular dysfunction, neurological disease or alcohol dependence.

Breath alcohol concentration (BrAC) was measured with the Dräger Alcotest 6510 (Drägerwerk AG & Co. KgaA, Lübeck, Germany), which is endorsed by the Swiss Federal Roads Office (FEDRO) for BrAC testing and is accurate to within 5%. Subjects drank water before each BrAC test to remove residual ethanol from their mouths. They were instructed to inspire deeply and then expire slowly into the detector until signalled to stop. The vHIT was administered as described in [16]. Twenty passive impulses were delivered pseudorandomly by the examiner to the right and left sides at velocities between approximately 200 and 300 deg/sec. VOR gain was expressed as a ratio of mean eye to head velocity. The cumulative

amplitude of overt catch-up saccades occurring after each impulse (i.e. all saccades seen after the head movement) was calculated and averaged across all trials (impulses) to the respective side. SVA was measured with custom equipment as described in [25] and expressed in logMAR units. DVA was then recorded for the left and right sides separately during passive head impulses directed from the side to the centre. Trials were accepted when head velocity reached a minimum of 150°/s, at which time the Landolt-Ring was presented for 100ms. DVA was also measured in logMAR units, but expressed as the difference between performance during static and dynamic conditions (SVA-DVA or “VA loss”), with larger values representing greater loss of acuity under dynamic conditions [25].

The participants did not eat or drink for six hours before drinking ethanol. They first underwent a baseline, pre-ethanol test recording of BrAC, vHIT and SVA/DVA. Following this, each subject consumed their first dose of ethanol. Standardized drinks of 40% alcohol by volume (ABV) were offered with some snacks; each drink (4cl) contained ~12.6g ethanol. The same tests were repeated 15 min after the first round of ethanol consumption. The 15 min time delay controlled for potential contamination of the BrAC recording by residual ethanol in the mouth. Subjects then consumed their next dose. This procedure was repeated until the subject chose to end their participation (or the maximum BrAC of 1.5 ‰ (per mill) was reached, which did not occur).

Results from the right and left sides were averaged for statistical analysis. The relationships between the independent variable (BrAC level) and dependent variables were assessed using a linear mixed effects regression with a random intercept representing individual subjects (Proc Mixed, SAS version 9.2, SAS Institute, Cary, NC). Separate models were fitted for each dependent variable.

Results

Subjects consumed between two and four drinks. At baseline BrAC was 0 ‰ for all subjects. The maximum BrAC reached for each subject ranged from 0.68 to 1.38 ‰ (mean 1.0 ‰).

Video head impulse test

Before ethanol intake all 8 subjects had normal VOR function on both sides, with mean VOR gain of 1.07 ± 0.12 (mean ± SD) and only few catch-up saccades (figures 1A, 2A). The cumulative overt catch-up saccade amplitude at baseline was very small (mean 0.13° ± 0.12°, figures 1A, 2B, 3). With increasing BrAC the VOR gain decreased significantly (to 0.80 ± 0.12 at maximal BrAC, a mean decrease of 0.27, effect size d = 2.3, 95% confidence interval (CI) -0.35 to -0.18, $p < 0.0001$, figures 1B and C, 2A). The change in gain was symmetric (asymmetry was 0.06 ±0.03 at baseline and 0.06 ± 0.05 at maximal BrAC). After ethanol consumption catch-up saccades became significantly larger and much more frequent. The cumulative overt catch-up saccade amplitude increased to 1.43° ± 0.58° at maximal BrAC (an increase of 1.30°, d = 3.1, 95% CI 0.86 to 1.54, $p < 0.0001$, figures 1B and C, 2B), and the peak latency of the saccades was between 200 and 300 msec after head impulse onset (figure 3). VOR gain and saccade amplitude were highly correlated ($r = -0.83$, $p < 0.05$).

Static and dynamic visual acuity

At baseline all subjects had normal SVA with a mean acuity of -0.15 ± 0.10 logMAR (figure 2C). DVA was also within the normal range at baseline (VA loss of 0.3 ± 0.17 logMAR, figure 2D). After ethanol intake DVA deteriorated significantly ($p = 0.0001$), while SVA did not change: Mean SVA levels after ethanol were -0.10 ± 0.13 logMAR (a change of 0.05 logMAR, 95% CI -0.05 to 0.14, $p = 0.29$). VA loss values increased to 0.56 ± 0.14 logMAR (i.e. by 0.24 logMAR, d = 1.7, 95% CI 0.14 to 0.34) indicating significantly greater loss of DVA with increasing intoxication. The correlation between VOR gain and VA loss was significant ($r = -0.75$, $p < 0.05$).

Discussion

We have shown that ethanol consumption produces a dose-dependent, symmetric deterioration of the VOR in normal volunteers. With increasing levels of intoxication, there was a significant decrease in VOR gain and an increase in the number and size of catch-up saccades, indicating that volunteers had diminishing ability to keep their eyes on target during rapid unexpected head movements and instead used increasingly larger voluntary saccades to maintain gaze. This deficit was accompanied by a significant decrease in visual acuity during head movements, while vision under static conditions remained unaffected.

vHIT versus DVA

Our results show that both the vHIT and DVA tests are similarly able to determine VOR function, as has been previously shown in age-dependent testing of normal subjects [25]. The study showed that vHIT and DVA measurements are highly correlated, similar to the established relationship between DVA and HIT recorded with search-coils, the gold standard for measuring eye movements [25]. The vHIT and DVA tests have previously been evaluated in patients with varying degrees of vestibular failure, showing a correlation between disease severity and test performance [16, 25]. In contrast, the repeated measures design employed in the current study allowed us to track the evolution of progressive, experimental vestibular dysfunction caused by ethanol intoxication in the same subjects over the course of an evening. We recorded a dose-dependent change in all three vestibular-dependent measures: VOR gain, cumulative catch-up saccade amplitude and DVA. The results clearly illustrate the increasing need for voluntary saccades to supplement the VOR as gain decreases, and show that the decline in VOR gain was significantly associated with a functional deficit of vision during head movement. This provides additional validation of the DVA test [25] as a measure of vestibular function.

Dynamic versus static visual acuity

In accordance with previous studies [21, 22, 26], there was a difference between measures of static and dynamic visual acuity, whereby there were similar effects of ethanol on the vHIT and DVA but no significant changes in SVA. In contrast, another study using a similar method of ethanol ingestion described significant, small-moderate changes in SVA above 1 ‰ BrAC [26]. While we cannot rule out a small

effect of ethanol on SVA due to the small number of volunteers tested, our results suggest that any effect on SVA must be much smaller than the large effects shown for the vestibular-dependent tests.

Topographic considerations

For both the vHIT and DVA tests it is difficult to determine whether the ethanol-induced vestibular dysfunction is due to disruption of central versus peripheral function or the afferent versus efferent loops of the vestibulo-ocular system. Ethanol can potentially affect many parts of the nervous system: the peripheral sensory organs and pathways, central neural structures such as the cerebellum, including the cerebello-spinal, cerebello-vestibular and spino-cerebellar tracts, cognitive and behavioural systems and especially the vestibulo-ocular system. In the central nervous system, Purkinje cells are known to be highly sensitive to ethanol [20, 23], but the primary sensory pathways, e.g. the lateral geniculate nucleus neurons of visual system [18], seem to be relatively unaffected. Different parts of the vestibular system may be individually vulnerable to ethanol exposure, for example the inhibitory effect on synaptic transmission in vestibular neurons differs between the lateral and medial vestibular nucleus [13]. The peripheral organs are also thought to be directly affected as shown by the presence of ethanol-induced positional nystagmus [9].

Thus the diminished gain in the vHIT could be caused by either decreased sensitivity of the peripheral receptors or impaired excitability of the vestibular nerve or its central connections. The changes seen on the vHIT in this study were typical of those seen in patients with peripheral vestibular lesions, such as those caused by vestibular neuritis [27]. But similar responses have also been shown in patients with peripheral nerve and central lesions (e.g. those associated with vestibular schwannoma [28] or cerebellar ataxia [14]). Since we mostly observed overt saccades in our subjects (at a peak latency between 200-300 msec), and not covert saccades (which occur during the head movement and can develop with increasing exposure to the test), this might suggest that central pathways were more affected, decreasing the capability for saccadic compensation. Despite our inability to exactly determine the contributing parts of the system, we hypothesise that, given the evidence for significant central effects of ethanol, the ethanol-induced vestibular hypofunction probably arises predominantly from the central part of the vestibular system.

Methodology

In clinical studies it is difficult to reach comparable blood alcohol concentration (BAC) or BrAC levels, even with a fixed dose among a homogeneous group of subjects, because ethanol clearance depends on many factors, such as diffusion gradients, body mass index and body fat concentration, and ethanol dehydrogenase activity/induction with its individually different isoenzymes. In this study we aimed to track the deterioration of several measures of VOR function over consecutive measurements and thus allowed subjects to consume individualised total amounts of ethanol and attain different BrAC levels. In order to reach effective levels of BrAC, subjects drank consecutive standard portions of high proof ethanol drinks until they reached their preferred limit. While some studies measured BAC, this method was considered too invasive for the current study given that up to 4 samples per subject were required. However, given that BAC is well-estimated by BrAC ($r = 0.94$; [31]), this is unlikely to have affected the results.

Conclusion

Ethanol consumption systematically impaired the VOR to high-acceleration head impulses. The effect was highly consistent and was evident on both direct and indirect measures of VOR function. The vHIT showed diminished gain and increased frequency and size of overt catch-up saccades, while the DVA test showed a loss of visual acuity compared to that measured under static head conditions. The vHIT and DVA tests are both non-invasive measures of the high-acceleration VOR, and can be administered repeatedly to track the evolution of VOR function during experimental manipulation or in clinical contexts. Our results illustrate a gradual, but systematic decline in VOR function with increasing levels of intoxication in otherwise normal volunteers.

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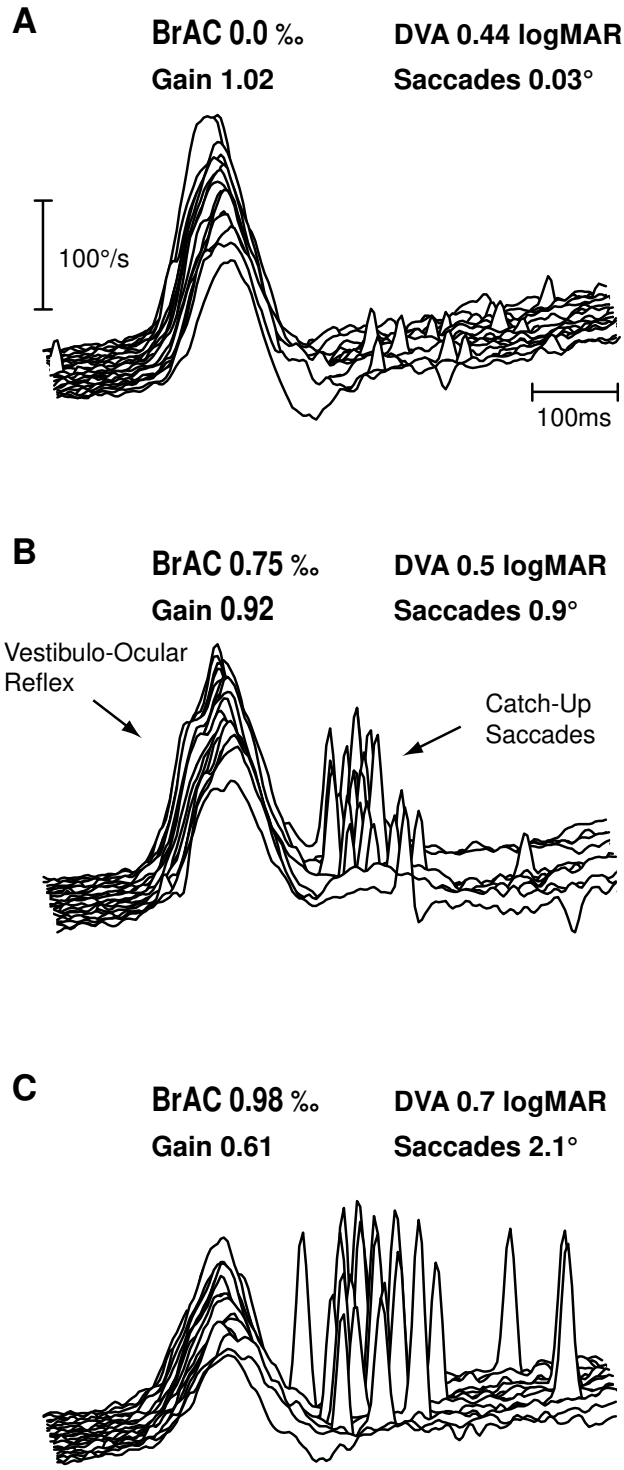
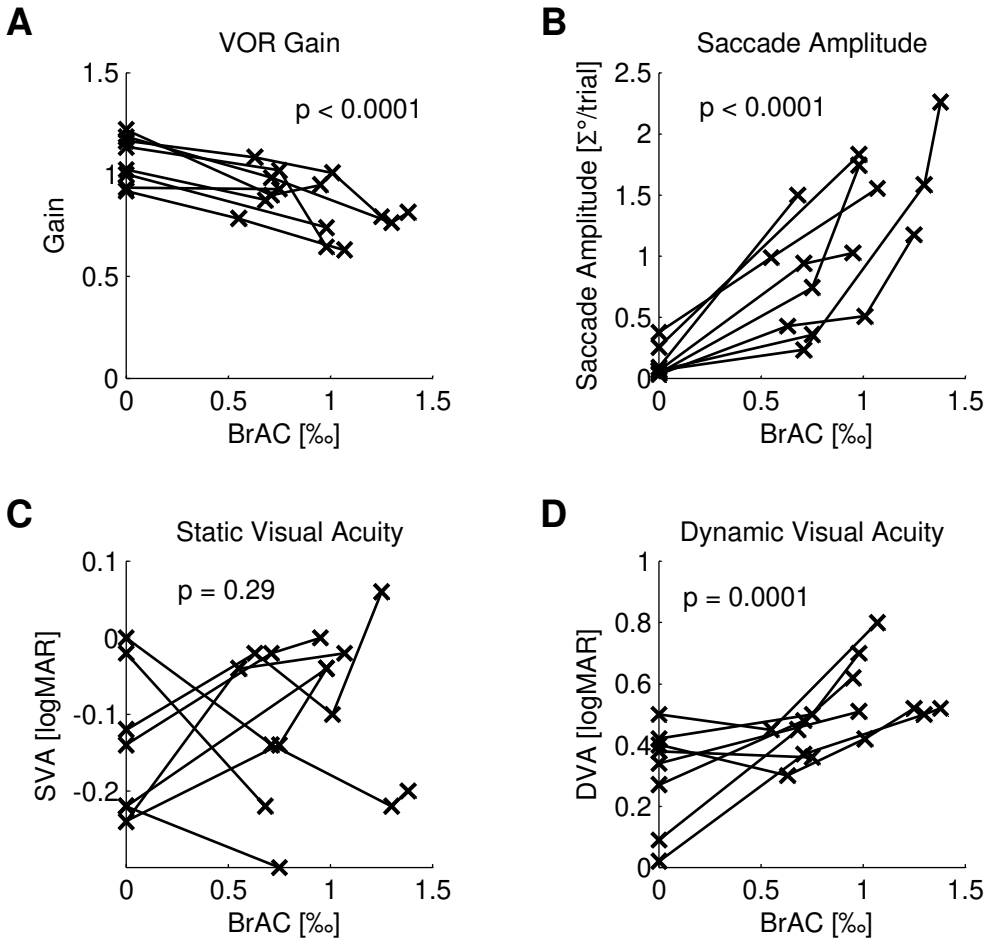
Tables and Figures

Figure 1: *Repetitive video head impulse testing with increasing breath ethanol content.*



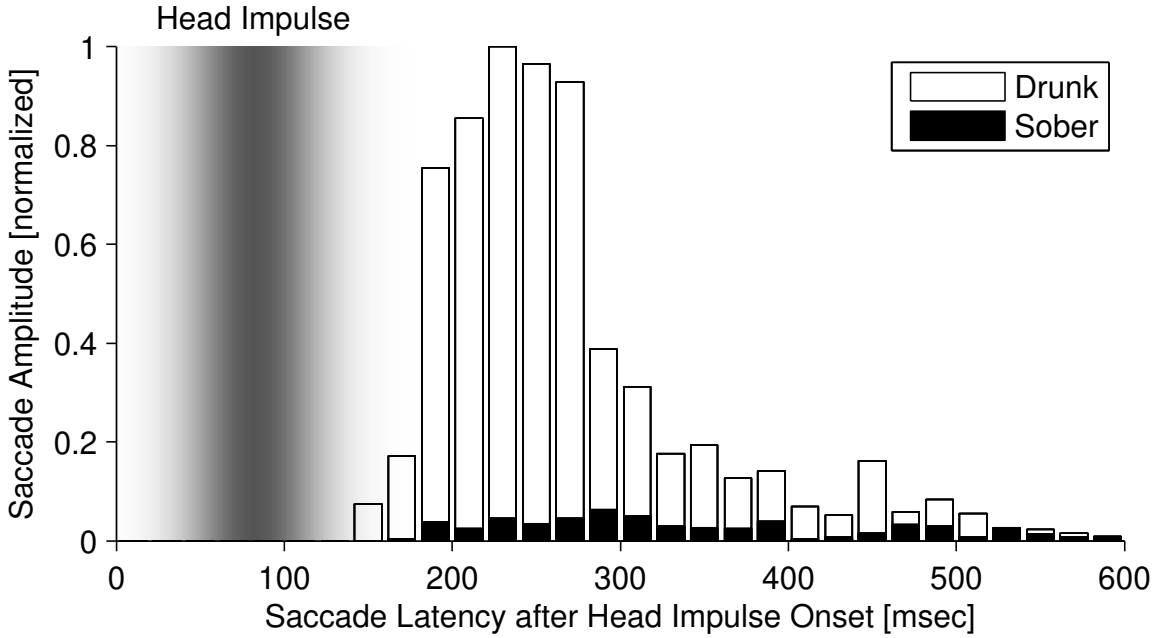
A) At baseline the subject had a left-sided vestibulo-ocular reflex with normal gain and almost no catch-up saccades. B) and C) With increasing breath alcohol concentration (BrAC) the VOR gain decreased, while compensatory catch-up saccades increased in number and amplitude. At the same time dynamic visual acuity deteriorated substantially, reflected by increasing VA loss values.

Figure 2: *Video head impulse test (A, B) and static (C) and dynamic (D) visual acuity measurements as a function of breath alcohol concentration (BrAC).*



The gain of the vestibulo-ocular reflex (A) decreased with rising BrAC while cumulative catch-up saccade amplitude (B) increased, indicating a deterioration in vestibulo-ocular reflex function. While static visual acuity (C) remained unchanged, dynamic visual acuity (D) deteriorated significantly with increasing BrAC. Data (x) from individual subjects are connected with thin lines.

Figure 3: *Cumulative amplitude of overt catch-up saccades before and after ethanol intake.*



Before ethanol consumption there were only few small catch-up saccades (shown by the filled bars). In contrast, after ethanol consumption large overt saccades emerged (empty bars), with latency peaking between 200 and 300 msec after head impulse onset (0 ms). The grey gradient represents the time course of the impulse, with the darkest region showing the peak head velocity. The histogram bars represent amplitudes of overt saccades summated across all subjects and organized in 20 msec bins . Filled bars contain data from head impulses to both sides in all subjects at baseline (n = 8 × 2 sides). Empty bars show data from the last measurement after ethanol consumption (i.e. at each subject's maximal BrAC level). Saccade amplitude was normalized to the largest histogram bar in the maximal BrAC condition.